

**Administration of Subanesthetic Dose of Ketamine and Electroconvulsive Treatment on
Alternate Week Days in Patients with Treatment Resistant Depression: A Double Blind
Placebo Controlled Trial**

Murat Altinay, MD; Roman Dale, MD; Amit Anand, MD; Adrienna Winters, BS; Nora Finnegan,
RN; Lawre Stratton RN; Jeff Klopp, R.Ph.; Michael Parsons, Ph.D.; Kelly Angle BA, Stephen
Jones, MD, PhD. Mark Lowe, PhD. and Nathan Kearns, BA.

A. SPECIFIC AIMS

1. Overall Aim:

Major Depressive Disorder (MDD) is one of the most prevalent psychiatric disorders (10 -15% prevalence). Patients who fail to respond to at least two antidepressant trials in their current depressive episode are considered to have Treatment Resistant Depression (TRD). The monoamine hypothesis can only partially explain the pathophysiology of depression and currently available antidepressants fail to be effective in significant portion of patients who have TRD. There is a growing clinical evidence that glutamate metabolism is one of the mechanisms that underlies the pathophysiology of depression (1, 2). In addition to depression, glutamate also seems to regulate learning and memory through its role in long term potentiation in the hippocampus (3, 4) .

Electroconvulsive Therapy (ECT) is one of the safest, most effective and robust treatments for TRD, however there is a growing need for new treatment options for patients who have failed to respond to ECT. Moreover, high relapse rates after discontinuation, cognitive side effects associated with the treatment and possible treatment resistance have made researchers seek alternative treatment options.

The role of ECT in glutamate regulation seems to be complex and not fully understood. While it increases glutamergic activity in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex, this effect was not shown in hippocampus (5-7). Moreover, several animal studies

demonstrated that electroconvulsive shock (ECS) therapy in animals caused decrease in NMDA-NR2B expression which is associated with memory function (8-10).

An imaging study done by Nobler and colleagues supported some of the findings above. ECT was shown to decrease glucose metabolism in widespread regions including left medial temporal lobe, which plays a major role in memory(11).

N-Methyl-D-Aspartate (NMDA) channel blockers, especially ketamine, was shown to elicit a rapid (1-5 hours) antidepressant response when administered in sub-anesthetic repeated doses. In addition to this rapid effect, ketamine's antidepressant effects were shown to remain in effect beyond its half-life, for at least 48 hours or more (12-17) The underlying mechanism of this effect seems to be through increasing metabolic activity in temporal and parietal cortex, mid-cingulate cortex and hippocampus while decreasing activation in subgenual cingulate (13). It has been hypothesized that ketamine's effect may be mediated by its effect on other glutamate receptors such as the AMPA and kainate receptors (18). NMDA receptor blockade may lead to increased release of post-synaptic glutamate which would then act on AMPA and kainate receptors. This action has been shown to increase dopamine release in the striatum and frontal cortex which may be related to ketamine's antidepressant response.

The differential effects on the NMDA and non-NMDA receptors may explain the efficacy and side-effect profile of ECT and ketamine. The increased NMDA receptor related glutamergic neurotransmission by ECT may lead to memory impairment while ketamine's NMDA blocking properties may lead to enhancement of cognition(19). On the other hand, the increased non-NMDA receptor mediated glutamergic neurotransmission caused by both ECT and ketamine may be related to their antidepressant response. It follows therefore that a combination of ketamine and ECT treatment may be synergistic in the treatment of resistant depression while not causing significant memory impairment.

Indeed, data from retrospective/non-randomized studies also suggest that when used as an anesthetic agent, ketamine causes faster reorientation after ECT (18) and improves word recall measured after 6 ECT treatments(20). Ketamine's rapid antidepressant effect and its positive

effect on memory and cognition led researchers to design studies to assess if pre-ECT ketamine could reverse ECT induced memory impairment and enhance antidepressant effect in patients with TRD. In a previous study, Abdallah and colleagues demonstrated that ketamine infusion at dose of 0.5mg/kg, given just before ECT did not enhance antidepressant effect (21). The negative result of this study, however, could possibly be related to ketamine being given too close to the time of ECT administration. ECT's acute profound effects on NMDA neurotransmission may negate or dilute ketamine's ameliorating NMDA antagonistic effects or synergistic effects on the non-NMDA receptors. As it takes at least 24 hours to recover from ECT immediate effects it follows that ketamine should be administered 24 hours after ECT.

During a treatment course ECT is usually given on alternate days. In this proof of concept study, we propose to administer ketamine also on alternate days interleaved with ECT days. Our hypothesis is that interleaved ketamine treatment will enhance ECT effects, decrease the number of ECT treatments needed to achieve response and remission and reduce cognitive impairment due to ECT.

Specific Aim:

In light of the current literature on the antidepressant and cognitive effects of ECT and ketamine, our aim is to show that administering ECT and ketamine on alternate weekdays will lead to a greater decrease in the depression scores along with less cognitive impairment due to ECT.

The study will compare the effects of standard 0.5mg/kg ketamine dosing with an active placebo arm where midazolam (0.045mg/kg IV over 40 minutes) will be used. This medication has recently been used as a placebo in other clinical trials (14-17, 21) when using ketamine for TRD. It causes sedation which would be similar to the effect of ketamine, but at the same time, its effects are time limited to the duration of the infusion and therefore will not interfere with cognitive testing or ECT effects.

In severe treatment resistant depression, the pathway integrity of BSMN will be altered. Our goal is to combine these pathway measurements into an index of connectivity - anatomic impairment-functional connectivity index (AIFCI), which will have greater sensitivity and specificity than either functional connectivity (F_c) or structural connectivity (S_c) alone.

Hypothesis 1:

We hypothesize that interleaved ECT and active ketamine treatment will lead to a meaningful clinical improvement as measured with the Clinical Global Impression for Improvement (CGI-I) scale and a greater decrease in depression scores as measured with the 17-item Hamilton Depression Rating Scale (HDRS) and Montgomery Asberg Depression Rating Scale (MADRS), compared to ECT and placebo treatment arm.

Hypothesis 2:

We hypothesize that interleaved ECT and active ketamine treatment will attenuate cognitive side effects compared to ECT and placebo treatment arm, as measured with the Montreal Cognitive Assessment (MOCA), Hopkins Verbal Learning Test – Revised (HVLT-R), and Self-Reported Global Self Evaluation of Memory.

Hypothesis 3:

We hypothesize that in TRD patients, functional connectivity between BSMN and respective targets NAcc and AMYG will be decreased.

B. RESEARCH STRATEGY

1. Significance

- a. Major Depressive Disorder (MDD): MDD is one of the most prevalent psychiatric illnesses (10 -15% prevalence). Patients who fail to respond to at least two medication trials are considered to have TRD. ECT is one of the safest and most effective treatments indicated for the treatment of TRD; however, high relapse rates after discontinuation, cognitive side effects associated with the treatment and possible treatment resistance have made researchers seek alternative

treatment options. Intravenous ketamine, an emerging alternative treatment for TRD is considered to be a promising treatment option. However, to date, there is no consensus in regard to an algorithm should be in treating TRD, nor guidelines to help clinicians identify patients who are more or less likely to respond or fail specific treatments.

By assessing the effects of ketamine when combined with ECT we aim to identify whether ketamine augmentation of ECT response can lead to a greater improvement in depression symptoms and reduction in memory impairment. In long term, the data obtained from the proposed proof of concept study will be used to design a larger scale study, which could potentially provide valuable data in the development of an algorithm of TRD treatment.

2. Methods and Design:

Patients with TRD who are deemed to be eligible for ECT treatment will randomly be assigned to either a subanesthetic dose of ketamine (0.5 mg/kg) or active placebo (midazolam) on week days that they don't receive ECT treatment.

a. Standard Dose Ketamine Group

Patients who are randomized to be on this group will receive a standard dose of ketamine (0.5mg/kg infusion over 40 min period) in accordance with research studies that have used ketamine as an antidepressant(22).

The patients will receive ECT treatment on Mondays, Wednesdays and Fridays for a total of 9 sessions. They will receive ketamine infusion on remaining week days for a total of 6 ketamine infusions.

b. Active Placebo Group

Patients who are randomized to be on this group will receive midazolam 0.045mg/kg IV over 40 minutes

The patients will receive ECT treatment on Mondays, Wednesdays and Fridays for 9 sessions. They will receive midazolam infusion on remaining week days for a total of 6 midazolam infusions.

c. ECT Treatments

All patients (independent of their depression scores) will receive the same ECT parameters: Bi-frontal (BF) brief pulse (0.5 msec) ECT administered by using Thymatron ECT machine.

Study blinding:

Neither the patients, nor the treating psychiatrist or the nurse will be aware of the patient's assigned arm. An unblinded pharmacy personnel will provide the team with the infusion bag before each infusion. The success of blinding will be tested after each ketamine treatment with a questionnaire given to the subject, raters, and treating physician.

d. Functional Neuroimaging

All subjects who meet the inclusion criteria will be offered a separate imaging consent. For patients who are willing to participate, will undergo functional and structural magnetic resonance imaging (MRI) at baseline and 3 weeks after completion of the study procedures. The study aims to compare functional and structural differences between five (5) patients with treatment resistant depression (TRD) and five (5) healthy controls (HC) at baseline and after 3 weeks of interleaved ECT and iv ketamine or active placebo (midazolam) treatment.

3. Recruitment and Timeline

a. Recruitment

Patients with TRD who are admitted to the inpatient psychiatric to receive an acute series of ECT at the Cleveland Clinic Lutheran Hospital will randomly be assigned to one of the study arms described above.

b. Timeline

Five patients will be recruited to each study arm over a 12 month period.

4. Rating Scales:

1- Diagnostic and Symptom Rating Instruments:

- a. Clinical Global Impression of Improvement Scale (CGI-I)**
- b. M.I.N.I. Plus (Mini Neuropsychiatric International Interview) (Scale English Version 5.0.0)**
- c. Montgomery Asberg Depression Rating Scale (MADRS)**
- d. Hamilton Depression Scale (HAM-D-17)**
- e. Neuroticism/Extraversion/Openness- Five Factor Inventory (NEO-FFI)**
- f. Hamilton Anxiety Rating Scale (HAM-A)**
- g. Columbia Suicide Severity Rating Scale (CSSRS)**
- h. LIFE-RIFT (Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool)**
- i. Young Mania Rating Scale (YMRS)**

2- Neuropsychological Testing Instruments

- a. Montreal Cognitive Assessment (MOCA)**

- b. Hopkins Verbal Learning Test – Revised (HVLTR)**
- c. Self-Reported Global Self Evaluation of Memory**
- d. Controlled Oral Word Association Test (COWAT)**
- e. Trail Making Test, Part A**
- f. Trail Making Test, Part B**

3- Assessment of Blind Questionnaire

Baseline assessments: All patients will receive M.I.N.I., MADRS, HAM-D-17, YMRS, NEO-FFI, HAM-A, CSSRS and LIFE-RIFT as part of diagnostic/rating scale instruments.

For cognitive testing: MOCA as a global cognitive measure as well as COWAT (for verbal fluency), Trail Making Tests (for processing speed and executive function) and HVLTR (for memory) are objective measures of cognitive function. Patient reported cognitive symptoms will be evaluated with the Self-Reported Global Self Evaluation of Memory.

Study Visit Assessments: Before each infusion, the patients will receive MADRS, HAM-D-17, HAM-A, CSSRS, LIFE-RIFT, YMRS and CGI-I.

After 4th and 9th (last) ECT treatment (Visits 9 and 17) the patients will receive MOCA, HVLTR, and Self-Reported Global Self Evaluation of Memory.

Assessment of Blind Questionnaire: To assess the success of blinding, at Visit 17, the patients will be asked to guess which study arm they had been assigned to.

A psychometrist from Cleveland Clinic Department of Neuropsychology, Nathan Kearns, will train the study coordinator on administering the rating scales and the neuropsychological testing instruments under supervision of Michael Parsons. The primary investigator and the study coordinator will be responsible for the administration of all the rating scales and the neuropsychological testing instruments.

To prevent practice effects on cognitive tasks and memory measures, different versions of these tests will be used where possible (MOCA, COWAT, HVLT-R).

Post-Study Assessment and Procedures: Once patients have completed all of the study procedures, they will be offered the option to receive open-label ketamine infusions and/or ECT treatments if it's clinically necessary. During this phase, patients will be given symptom severity scales (CGI-I, MADRS, HAMD-17, HAM-A, CSSRS, LIFE-RIFT, YMRS) to monitor their progress.

5. Schedule of Visits

	Screening & Randomization	Baseline	Visit-1	Visit-2	Visit-3	Visit-4	Visit-5	Visit-6	Visit-7	Visit-8	Visit-9 (Post ECT-5)	Visit-10	Visit-11	Visit-12	Visit-13	Visit-14	Visit-15	Visit-16	Visit-17
Main study visits																			
Treatments			ECT1	Infusion-1	ECT-2	Infusion-2	ECT3	ECT4	Infusion-3	ECT5		Infusion-4	ECT-6	ECT-7	Infusion-5	ECT-8	Infusion-6	ECT-9	
Informed Consent	X																		
Pretreatment Assessment (1)	X																		
Symptom Rating Scales (2)		X		X		X			X			X			X		X		
Neuropsychological Tests (3)*,		X									X								X
Blinding Questionnaire																			X

1. M.I.N.I. Plus, MADRS, HAMD-17, NEO-FFI, HAM-A, CSSRS, LIFE-RIFT, YMRS

2. MADRS, HAMD-17, HAM-A, CSSRS, LIFE-RIFT, YMRS, CGI-I

3. MOCA, HVLT-R, Self-Reported Global Self Evaluation of Memory, COWAT, Trail Making Test Parts A & B.

*: Post ECT Neuropsychological tests will be administered on the day following the ECT treatment.

6. Inclusion Criteria

1. Males/females at least 18 years of age but no older than 60 years of age
2. Meet DSM-IV criteria for Major Depression or Bipolar Disorder, depressed phase, as determined by a clinician's diagnostic evaluation and confirmed by interview using the Mini International Neuropsychiatric Interview (MINI PLUS 5.0.0)
3. A current depressive episode that has lasted a minimum of 4 weeks.
4. Meet the following criteria on symptom rating scales at screening:
 - a. Hamilton Depression Scale (HAM-D 17) >18
 - b. Young Mania Rating Scale (YMRS) of ≤ 10
 - c. Montreal Cognitive Assessment (MoCA) of ≥ 23
5. Screened for temperament and co-morbid anxiety using the Neuroticism/Extraversion/Openness – Five Factor Inventory (NEO-FFI) Scale, and the Hamilton Anxiety Rating Scale (HAM-A)
6. Have ≥ 3 trials of antidepressants/augmentation strategies.
7. Have a support system capable of transporting the patient post-treatment.

7. Exclusion Criteria

- a. Meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, mental retardation, pervasive developmental disorder.
- b. Meeting DSM-IV criteria for other substance/alcohol dependence within the past 6 months or abuse in the past 3 months.
- c. Patients who meet exclusion criteria for ketamine and/or midazolam infusion.

8. Exclusion Criteria for ECT Treatment

- a. Acute or chronic medical or neurological illness that would be a contraindication for ECT treatment.

- b. Unstable or severe cardiovascular conditions such as recent myocardial infarction, unstable angina, poorly compensated congestive heart failure, and severe heart disease,
- c. Aneurysm or vascular malformation that might be susceptible to rupture with increased blood pressure,
- d. Increased intracranial pressure, as may occur with some brain tumors or space-occupying cerebral lesions,
- e. Recent cerebral infarction,
- f. Pulmonary conditions such as severe chronic obstructive pulmonary disease, asthma or pneumonia,
- g. Patient status read as ASA level 4 or 5

9. Exclusion Criteria for Ketamine Treatment

1. History of significant suicidality / impulsivity that would place the patient at risk to participate in this protocol as assessed clinically and by the Columbia Suicide Screen Rating Scale (CSRSS)
2. Presence of psychotic symptoms at any point in their psychiatric history or positive screen using abridged version of the Community Assessment of Psychic Experience Scale (CAPE)
3. History of current Substance Use Disorders (need > 1 year sobriety)
4. History of Dissociative Disorder or Conversion Disorder
5. Primary Axis II (Personality Disorder) diagnosis
6. Co-morbid and currently uncontrolled Panic Disorder.
7. Co-morbid and currently uncontrolled Post Traumatic Stress Disorder
8. Co-morbid and currently uncontrolled Obsessive-Compulsive Disorder
9. History of CNS disease or injury
10. Women who are pregnant or breastfeeding
11. Mental Retardation, or a total IQ score of ≤ 85 , or having a Guardian
12. Severe respiratory or cardiovascular disease.
13. Known allergic response to ketamine.

10. Exclusion Criteria for Midazolam Treatment

1. Previous intolerance or hypersensitivity to midazolam.
2. It is also contraindicated in acute narrow glaucoma and concurrent use of potent inhibitors of CYP3A4 (amprenavir, atazanavir, or ritonavir).

11. Exclusion Criteria for Functional and Structural MRI

- a. Current pregnancy or breast feeding.
- b. Metallic implants or other contraindication to MRI.

12. Early Remission

In the event that the patients achieve remission (HAM-D<8) before all of the study visits have been completed, the patients will be scheduled for 3 more ECT visits and infusions. If the HAM-D scores are below 8 on all 3 ECT visits, the patient will no longer be given ECT treatments. If HAM-D scores remain ≥ 8 , they will continue receiving ECT treatments and infusions.

13. Informed Consent

Patients who are eligible will be asked to sign a written informed consent form and will be advised of all the potential medication side effects if they participate in the study, regardless of their group assignment.

14. Potential Risks

Since the initial RPC application we have received IRB approval as well as obtained FDA IND exemption to conduct this study.

Risks associated with this study are those associated with the interview for psychiatric symptoms, anesthesia, potential delay in treatment, antidepressant treatment and loss of confidentiality.

a. Interview for psychiatric symptoms

Some patients may become anxious when they focus on their symptoms.

b. Risks associated with ECT Treatment

i. Anesthesia:

- **Headache, confusion, delirium**

ii. Cognitive Side Effects:

- **Short term memory loss:** Memory loss is the most common side effect of the ECT treatment. 75% of the patients who receive ECT treatment experience short term memory loss. Most of the patients return to their baseline after 6 months however, some patients complain about persistent memory loss.

iii. Other risks

- **Fractures-** The risk is low compared to the early days of the treatment; with routine use of muscle relaxants.
- **Muscle soreness**
- **Nausea, vomiting**

c. Risks Associated with ketamine Infusion

i. Arrhythmia

- Bradycardia
- ii. Tachycardia
- iii. Hypertension
- iv. Hypotension
- v. Hypoventilation
- vi. Apnea
- vii. Enhanced skeletal muscle tone (i.e., tonic-clonic movements)
- viii. Anaphylactic or other allergic reactions
- ix. Hallucinations or other emergence reactions (i.e., confusion, delirium, irrational behavior)

d. Risks Associated with Midazolam Infusion

- i. Drowsiness, over sedation, headache
- ii. Nausea, vomiting
- iii. Pain and local reactions at injection site
- iv. Cough
- v. Decreased tidal volume and/or respiratory rate decrease
- vi. Anterograde amnesia
- vii. CNS depression
- viii. Hypotension
- ix. Paradoxical disinhibition
- x. Respiratory Depression

e. Interactions Between ECT and Ketamine

Studies published to date have used Ketamine as an anesthetic agent for ECT (19, 21, 22). In these studies, ketamine was well tolerated as an anesthetic agent and there were no reported negative effects of ketamine on seizure duration and quality. One study (23) showed that patients who received Ketamine adjuvant to propofol as an anesthetic agent for ECT showed marked restlessness and disorientation compared to patients who received propofol and saline infusions. We don't anticipate this to be an issue in the proposed study, for the treatments will be given on alternate days.

f. Interactions Between ECT and Midazolam

Midazolam was used in several research studies to assess the effects of benzodiazepine administration prior to ECT. In these studies, midazolam was well tolerated with no reported adverse effects. One study (24) showed that midazolam did not have any influence on seizure threshold; however, patients needed higher dosages of muscle relaxants and anesthetic dosages after midazolam was discontinued. In contrast, several other studies showed that midazolam decreased seizure duration, while shortening post ECT delirium and agitation (25-28). We don't anticipate seeing these changes in the proposed study, for the treatments will be given on alternate days.

g. Interactions Between Flumazenil and Ketamine

There no known interactions between ketamine and flumazenil. One study (29) that investigated subanesthetic ketamine on flumazenil binding in humans showed that it did not affect flumazenil binding.

15. Protection Procedures

- a. Interview for psychiatric symptoms:** The psychiatric interview will occur as a standard evaluation process in an outpatient/inpatient setting. When a patient in an outpatient setting demonstrates worsening of symptoms which may

require inpatient hospitalization, there will be an opportunity to for admission and initiation/ continuation of the ECT treatment.

b. Risks associated with ECT Treatment

i. Anesthesia:

- **Headache:** Patients who experience headaches will be premedicated with ketorolac. Post ECT treatment headache treatment with NSAIDs will also be sought.
- **Confusion, delirium:** Confusion is a common side effect for patients coming out of anesthesia and could be treated with barbiturates and benzodiazepines. If delirium occurred, appropriate medication adjustments and/or inpatient hospitalization will be sought.

ii. Cognitive Side Effects: The degree of cognitive side effects is related to the amount of electrical stimulation used and the location of the treatment. For patients who experience persistent memory difficulties, stimulation parameters and location will be altered to minimize this side effect.

c. Potential delay in treatment: Lutheran Hospital has a very busy ECT service. Initiation of the ECT treatment may take up to a couple of weeks. If the patients' condition worsens, several different options will be available for them, one of which is inpatient hospitalization.

d. Risks Associated with ketamine Infusion

i. Monitoring patients: Patients will be monitored during the infusion and recovery phase:

- Vital Signs will be noted and recorded every ten minutes during the ketamine infusion.

- Oxygen saturation will be monitored using pulse oximetry.
 - Other monitored parameters will include cardiac rate and rhythm, respirations. The nurse will assess that the patient's response using the Ramsey Scale.
- ii. Emergency equipment shall be readily available to Hospital or medical staff during the recovery phase. The equipment will contain but not be limited to:
- external defibrillator
 - emergency medications
 - oxygen
- iii. Reversal Agent: There is no specific reversal agent for ketamine. The treatment of prolonged sedation or overdose is supportive. In the normal patient the drug effects will reverse in a short period of time given proper oxygenation.
- e. Risks Associated with midazolam infusion
- i. **Monitoring patients:** Patients will be monitored during the infusion and recovery phase:
- Vital Signs will be noted and recorded every ten minutes during the ketamine infusion.
 - Oxygen saturation will be monitored using pulse oximetry.
 - Other monitored parameters will include cardiac rate and rhythm, respirations. The nurse will assess that the patient's response using the Ramsey Scale.

ii. Emergency equipment shall be readily available to Hospital or medical staff during the recovery phase. The equipment will contain but not be limited to:

- Administration of reversal agent flumazenil
- external defibrillator
- emergency medications
- oxygen

16. Emergency Procedures

All study participants will have the contact information for the study coordinators and investigators who will be available during business hours (9 A.M. to 5 P.M.)

Study participants who need assistance after business hours will be directed to Cleveland Clinic “Meet Me Line” where an on-call psychiatry resident will assist the patient and notify the study coordinator and the investigators.

The unblinded pharmacist will prepare a sealed envelope which will have the information of the patient’s assigned study arm. This envelope will be readily available in the patient’s study binder. In case of an emergency, this envelope will be opened to break the blind.

17. Potential Benefits:

The risk/benefit ratio of the proposed study is favorable. Patients with MDD, severe and resistant to treatment will be offered one of the most effective treatments, ECT, for the treatment of their condition.

18. Importance of Knowledge to be gained

It is critical to treat patients who suffer from severe Major Depressive Disorder with treatment resistance and the current therapies that could be offered to this patient population is limited. If shown effective, the results of this study will provide an alternative way of managing the symptoms of patients with treatment resistant depression and improving the risk/benefit ratio for ECT.

19. Procedures and responsibilities for data capturing:

REDCap is being used to store data on a secure Cleveland Clinic desktop in locked offices on Lutheran 5E/P57. The computer is password protected. The REDCap system is maintained by QHS and the database within REDCap will be maintained by co-investigator & coordinator Adrienna Easterling. Adrienna Easterling, under the supervision of the principal investigator, Murat Altinay, M.D., is responsible for entering and maintain data. Patient identifiers will not be disclosed from any report or publication that may result for the study. All HIPPA and other applicable federal privacy laws will be followed.

20. Termination

After the patients complete the study, they will be followed by Dr. Roman Dale at Lutheran Hospital outpatient psychiatric clinic.

21. Imaging Analysis

1. RS-fMRI pre-processing: state-of the-art methods developed at the Cleveland Clinic Imaging Center will be used for motion-correction and physiological noise correction and images will be filtered at < 0.1 HZ.
2. DTI pre-processing: Diffusion-weighted images are corrected for motion and eddy currents using an iterative affine motion correction and diffusivities generated.
3. Region of interest and coregistration: The DRA and VTN will be identified on each subject individually with the help of an experienced neuroradiologist. The DRN are best identified on a sagittal MP2RAGE sequence at 7T, using inversion recovery. They are

visualize as a hypointense line along the posterior-superior aspect of the pons. The VTA are best seen on an axial GRE T2*, sliced through the level of the cerebral peduncles. There is a small protuberance into the interpeduncular cistern that is slightly T2* hyperintense, just lateral to the substantia nigra. This is roughly the target for the VTA. The identified DRA and VTN for each subject will then be used to calculate Sc (DTI) and Fc of with the rest of the brain and also with specific target regions of interest (ROIs). A priori target areas are at the ACC, NAcc, AMYG, and OFC.

4. Image analysis: Anatomic image data will be used to locate ROIs including VTA, DRN, NAcc, AMYG, sgACC, dACC, and OFC. DTI data will be used to quantify Sc in VTA-NAcc, VTA-AMYG, VTA-sgACC, VTA- OFC, DRN-AMYG, DRN-sgACC, and DRN-OFC node pairs. RS-fMRI data will be used to measure functional connectivity (Fc) along these pathways. The RS-fMRI- and DTI- derived pathway connectivity will be combined into a single functional metric: the anatomic impairment- functional connectivity index (AIFCI). The AIFCI, is composed of DTI measures of white matter Sc and RS-fMRI Fc measure of of DA and 5-HT pathways. This metric is a self-normalized measure of pathway integrity and is hypothesized to have greater specificity and sensitivity than either metric alone⁸ to differentiate between groups.

5. Statistical Analysis: Structural and functional connectivity maps between in depressed and healthy controls will be compared using a General Linear Model (GLM) in the Statistical Parametric Mapping (SPM) software. The AIFCI will be compared across groups using a one way ANOVA with age and gender as covariates.

6. Power Analysis: This is a pilot/proof of concept study with five subjects in each arm. The small number of subjects precludes any extensive power analysis. We will conduct conventional statistical analyses. Considering the small number of subjects these statistical analyses will mainly be used to examine for trends in the data and also to conduct a power-analysis for a future large-scale clinical trial and for grant applications to obtain funding for such a trial.

22. Statistical Analysis:

This is a pilot or proof of concept study with five subjects in each arm. The small number of subjects precludes any extensive power analysis.

The aim of the study is to be able to identify whether ketamine augmentation of ECT response can lead to a greater improvement in depression symptoms and reduction in memory impairment compared to ECT and placebo. To accomplish this aim, we have decided to use clinically meaningful measures to assess improvement in clinical symptoms and changes in cognitive impairment as our primary measures for this pilot study.

For clinical improvement we will use the CGI-I scale. CGI-I is a method developed to assess physician reported global functioning of patients before and after an intervention (30). In this study, CGI-I scores less than 4 will be considered as positive improvement.

To evaluate cognitive side effects, the reliable change (RC) index, derived from the standard error of measurement (SEM) for each test in the battery for the cognitive tests (31) will be used. The RC index is a frequently used method in psychiatric and clinical neuropsychology research, to show whether or not a difference in test scores between two evaluations for a given subject is greater than would be expected by chance variability. RC index will be measured by subtracting the subject's pretest score (x_1), from the same subject's posttest score (x_2), which will be divided by the standard error of difference (S_{diff}) between the two test scores ($RC = (x_2 - x_1) / S_{diff}$). S_{diff} will be computed directly from the SEM ($S_{diff} = \sqrt{2(SE)^2}$). RC greater than or equal to 1.84 will be considered as likelihood of post test score reflecting a meaningful change ($p < .05$, two tailed). The advantage of using this statistical method is that the baseline level of performance of a given individual is accounted for. For each subject, the difference between the assessments will be coded (according to the RC index) as 1 (declined relative to baseline), 2 (improved relative to baseline), or 3 (not different).

Using the CGI-I a simple count of subjects with clinical improvement (CGI < 4 at the end of the study) and cognitive change as measured by the RC index (≥ 1.84) a simple count of subjects in active vs. placebo treatment will provide an indication whether ketamine augmentation of ECT will be beneficial to the patients. If we find that more patients with ketamine augmentation vs. placebo report clinical improvement and/or less cognitive

impairment, the pilot study will support our hypothesis and provide the rationale and data for a larger definitive study.

In addition, we will also conduct conventional statistical analyses. Considering the small number of subjects these statistical analyses will mainly be used to examine for trends in the data and also to conduct a power-analysis for a future large-scale clinical trial and for grant applications to obtain funding for such a trial.

Hypothesis 1: Analyses for response (<50% decrease in HDRS and MADRS scores from baseline) and remission (HDRS<8 MADRS<6) will be conducted using the last observation carried forward (LOCF) method for patients with early withdrawal and missing values. The purpose for using the LOCF method stems from the requirement of entering an end point value for each patient while calculating the overall remission rate. Chi-square test will be conducted for differences between the ketamine and placebo groups for difference in frequencies in response and remission.

Hypothesis 2: To evaluate the differential effect of active ketamine vs. placebo with respect to the outcome measures (HDRS scores) a repeated measures mixed-effect model will be used (SAS Proc GLIMMIX). The advantage of mixed effect model is that it can use all subjects even those with missing values to estimate model parameters under the assumption of ignorable attrition. Primary analyses will be conducted for the intention to treat (ITT) sample, defined as randomized patients who received at least one dose of medication and at least one post-baseline efficacy assessment.

Future studies and plans using the pilot data: The data collected in this study will be used to conduct a power analysis for a large scale definitive study of ketamine augmentation of ECT in TRD patients. Preliminary data from this preliminary study will be used in grant applications including NIH grant applications to conduct this large scale study. In these future studies we will investigate whether ketamine augmentation can lead to shorter hospital stay, better remission and response rates and less functional and cognitive

disability with ECT treatment. This will be highly significant and useful for the clinical treatment of treatment resistant depressed patients.

23. Expense Assumptions

a. ECT Treatment

ECT treatment will be covered by patients' insurance.

b. Ketamine and Midazolam Infusions

2 arms with N = 5 x 6 infusions (Total of 30 infusions in each arm).

Midazolam:

i. Drug cost only - for the Midazolam infusion would be \$2.00 per bag or \$60.00 for the whole trial

Ketamine:

i. Drug cost only - for the Ketamine infusion would be \$4.00 per bag or \$120.00 for the whole trial

c. Diagnostic, Rating and Neurocognitive Scales

Hopkins Verbal Learning Test-Revised is the only copyrighted test that will be used in this study.

HVLT-R intro kit: \$330

d. Imaging Expenses

Costs to be covered by funds requested from Radiology Department:

- 1- The use of 7T MRI for 10 study subjects
- 2- MRI technician time

24. Funding

The principal investigator has applied for a \$12,500 Research Programs Committees(RPC) Awards Program. Cleveland Clinic Center for Behavioral Health will match this amount for a total study cost of \$25,000. Imaging costs will be covered by Cleveland Clinic Imaging Institute.

REFERENCES

1. Mitchell ND, Baker GB. An update on the role of glutamate in the pathophysiology of depression. *Acta psychiatrica Scandinavica*. 2010;122:192-210.
2. Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nature reviews Drug discovery*. 2008;7:426-437.
3. Peng S, Zhang Y, Zhang J, Wang H, Ren B. Glutamate receptors and signal transduction in learning and memory. *Molecular biology reports*. 2011;38:453-460.
4. Myhrer T. Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. *Brain research Brain research reviews*. 2003;41:268-287.
5. Michael N, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B. Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychological medicine*. 2003;33:1277-1284.
6. Merkl A, Schubert F, Quante A, Luborzewski A, Brakemeier EL, Grimm S, Heuser I, Bajbouj M. Abnormal cingulate and prefrontal cortical neurochemistry in major depression after electroconvulsive therapy. *Biological psychiatry*. 2011;69:772-779.
7. Pfleiderer B, Michael N, Erfurth A, Ohrmann P, Hohmann U, Wolgast M, Fiebich M, Arolt V, Heindel W. Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. *Psychiatry research*. 2003;122:185-192.
8. Dong J, Min S, Wei K, Li P, Cao J, Li Y. Effects of electroconvulsive therapy and propofol on spatial memory and glutamatergic system in hippocampus of depressed rats. *The journal of ECT*. 2010;26:126-130.
9. Sartorius A, Mahlstedt MM, Vollmayr B, Henn FA, Ende G. Elevated spectroscopic glutamate/gamma-amino butyric acid in rats bred for learned helplessness. *Neuroreport*. 2007;18:1469-1473.
10. Fumagalli F, Pasini M, Sartorius A, Scherer R, Racagni G, Riva MA, Gass P. Repeated electroconvulsive shock (ECS) alters the phosphorylation of glutamate receptor subunits in the rat hippocampus. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2010;13:1255-1260.
11. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, Mann JJ. Decreased regional brain metabolism after ect. *The American journal of psychiatry*. 2001;158:305-308.
12. Ghasemi M, Kazemi MH, Yoosefi A, Ghasemi A, Paragomi P, Amini H, Afzali MH. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. *Psychiatry research*. 2014;215:355-361.
13. Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM. Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. *Archives of general psychiatry*. 2008;65:154-164.

14. Zarate CA, Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry*. 2006;63:856-864.
15. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biological psychiatry*. 2000;47:351-354.
16. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological psychiatry*. 2010;67:139-145.
17. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvatore G, Machado-Vieira R, Manji HK, Zarate CA, Jr. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of general psychiatry*. 2010;67:793-802.
18. Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive disorder. *CNS & neurological disorders drug targets*. 2007;6:101-115.
19. McDaniel WW, Sahota AK, Vyas BV, Laguerta N, Hategan L, Oswald J. Ketamine appears associated with better word recall than etomidate after a course of 6 electroconvulsive therapies. *The journal of ECT*. 2006;22:103-106.
20. Krystal AD, Weiner RD, Dean MD, Lindahl VH, Tramontozzi LA, 3rd, Falcone G, Coffey CE. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. *The Journal of neuropsychiatry and clinical neurosciences*. 2003;15:27-34.
21. Abdallah CG, Fasula M, Kelmendi B, Sanacora G, Ostroff R. Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. *The journal of ECT*. 2012;28:157-161.
22. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2011;14:1127-1131.
23. Jarventausta K, Chrapek W, Kampman O, Tuohimaa K, Bjorkqvist M, Hakkinen H, Yli-Hankala A, Leinonen E. Effects of S-ketamine as an anesthetic adjuvant to propofol on treatment response to electroconvulsive therapy in treatment-resistant depression: a randomized pilot study. *The journal of ECT*. 2013;29:158-161.
24. Conca A, al-Dubai Z, Konig P, Beraus W. Combining nefazodone and midazolam during ECT. *European psychiatry : the journal of the Association of European Psychiatrists*. 1999;14:360-362.
25. Mizrak A, Koruk S, Ganidagli S, Bulut M, Oner U. Premedication with dexmedetomidine and midazolam attenuates agitation after electroconvulsive therapy. *Journal of anesthesia*. 2009;23:6-10.
26. Liston EH, Sones DE. Postictal Hyperactive Delirium in ECT: Management with Midazolam. *Convulsive therapy*. 1990;6:19-25.
27. Shah PJ, Dubey KP, Watti C, Lalwani J. Effectiveness of thiopentone, propofol and midazolam as an ideal intravenous anaesthetic agent for modified electroconvulsive therapy: A comparative study. *Indian journal of anaesthesia*. 2010;54:296-301.
28. Loimer N, Hofmann P, Chaudhry HR. Midazolam shortens seizure duration following electroconvulsive therapy. *Journal of psychiatric research*. 1992;26:97-101.
29. Salmi E, Långsjö JW, Aalto S, Någren K, Metsähonkala L, Kaisti KK, Korpi ER, Hietala J, Scheinin H. Subanesthetic Ketamine Does Not Affect 11C-Flumazenil Binding in Humans. *Anesthesia & Analgesia*. 2005;101:722-725.
30. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry*. 2007;4:28-37.
31. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of consulting and clinical psychology*. 1991;59:12-19.